compositions described therein. Basis for these amendments may be found in the specification at page 8, line 3 through page 9, line 26. New Claim 67 has been added to define an embodiment of the compositions of applicants' invention. This claim finds basis in the Specification at p.9, line 21. Applicants respectfully request entry of this Amendment as they respectfully submit that it places the claims in better form for allowance or appeal.

The compositions of applicants' invention relate to freeze-dried pharmaceutical treatment compositions containing a fast release layer and a sustained release layer. The compositions provide both fast and sustained, or controlled, release of a pharmaceutically active agent for at least six hours and preferably for at least 1 to 3 days. The composition is particularly useful as a vaginal insert for treatment of vaginal diseases without requiring the administration of multiple doses. Surprisingly, the compositions of applicants' invention maintain their "dual nature" as a fast release/sustained release dosage form despite the fact that the fast release layer and sustained release layer are combined and mixed prior to rapid freeze-drying and lyophilization, rather than being maintained separately in two macroscopically discrete layers. The rapid freeze-drying during the production of the compositions of applicants' invention leads to the maintenance of their shape as well as to the formation of multiple fast release and sustained release layers, as the different layers are not permitted to settle and separate. This leads to better availability of the pharmaceutical actives within the area of administration as they are more evenly distributed throughout the product.

With regard to the Final Rejection rendered February 4, 2002, applicants respectfully acknowledge the withdrawal of the rejection of claim 27 under 35 U.S.C. 112.

The Final Rejection objected to the title of the application and requested a more descriptive title. Applicants respectfully request reconsideration of this objection in light of the foregoing amendment to the title, i.e., to "Freeze-dried Controlled Release Compositions and Methods of Making Same".

The Final Rejection rejected Claims 1 and 65 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 has been corrected to delete the numeral "(iii)" which inadvertently appeared in the claim. The term "metrondazol" in claim 65 has been corrected as it was an inadvertent typographical error and should have been

–metronidazole—. Applicants respectfully submit that the rejection under 35 U.S.C. 112 is therefore rendered moot and respectfully request reconsideration thereof.

The Final Rejection of February 4, 2002 maintained the rejection under 35 U.S.C. 102(b) of claims 1, 2, 6-9, 13-20, 22-24, 27-29, 35-38, 41-43, 45, 49-53 over Huber and newly added claims 56, 59-64 and claims 1, 2, 6, 7, 25 and 53 and newly added claims 56, 59, 60, 63 under Iwata et al. Applicants respectfully request reconsideration of these rejections in view of the foregoing amendments to the claims and the ensuing remarks.

> Applicants note that the Huber reference describes compressed oral tablets having:
>
> ***two discrete portions***, a rapid release portion and a slow release portion, each portion containing a specific quantity of specially prepared nitrofurantoin. Still more particularly, the present invention relates to ***a compressed pharmaceutical tablet***... [Huber, col. 1, l. 47-65] (emphasis added)

Thus, Huber relates to a compressed tablet suitable for oral administration having two discrete portions. Importantly, the tablet described in Huber contains no water and thus cannot be freeze-dried. Nor does Huber suggest or describe the compositions made by freeze-drying as described in the amended claims. In contrast, the compositions of applicants' invention are made by freeze-drying as set forth in the claims as amended. In view of this distinction, applicants respectfully request reconsideration of the rejection under 35 U.S.C. 102(b).

The Final Rejection of February 4, 2002 reiterated the rejection of claims 1, 2, 6, 7, 25 and 53 and newly added claims 56, 59, 60 and 63 under 35 U.S.C. 102(b) as being anticipated by Iwata et al. (XP-002162841). Applicants respectfully request reconsideration of this rejection in light of the foregoing amendments to the claims and the ensuing discussion.

Iwata et al. is an abstract of a study relating to a sustained-release double-layered progesterone suppository for luteal-support therapy. While Iwata et al. describes a vaginal suppository, it indicates that the inner layer of the suppository consists of a "stick" containing hydroxypropylcellulose, carbopol and crystalline cellulose as well. Nowhere does Iwata et al. suggest or describe a dosage form made by freeze-drying. Furthermore, Iwata et al. requires a macroscopically dual layer product, with an inner HPC and CP layer and an outer Witepsol W35-based layer. Iwata et al. does not suggest or describe a dosage form in which a fast release layer and a sustained release layer may be intermixed, but still permits two modes of release. Thus, the claims, as amended, are distinct from the dosage forms set

forth in Iwata et al. Applicants therefore respectfully request reconsideration of the rejection under 35 U.S.C. 102(b) in view of Iwata et al.

The Final Rejection further maintained the rejection of claims 1-53 and newly added claims 56-66 under 35 U.S.C. 103(a) as being unpatentable over Huber in view of Morella et al. and Gole et al., in further view of Conte et al. and Saslawski et al. The Final Rejection notes, in responding to applicants' argument that the combination of Huber with Morella et al. is insufficient to lead one of ordinary skill in the art to the compositions of applicants' invention, that "the rejection is based on a combination of references in addition to Huber and Morella et al.". The Final Rejection also states that substituting the metronidazole of Morella et al. for nitrofurantoin of Huber "because Morella et al. teaches these active agents as interchangeable". [Final Rejection, p. 4]. Further, the Final Rejection posits that

> Huber and Gole both teach compositions comprising a fast release layer comprising matrix forming agents, and Huber teaches gelatin and gums as matrix forming agents and Gole teaches gelatin, xanthan gum and amino acids as matrix forming agents. Thus, teaching the gums of Huber as xanthan gums and adding amino acids to the fast release layer of Huber would be within the skill of one in the art. [Final Rejection, p. 4].

Applicants respectfully request reconsideration of this rejection in light of the foregoing amendments to the claims and the ensuing discussion.

Applicants respectfully submit that the cited references, taken separately or all together, would not have lead one of ordinary skill in the art to the compositions of applicants' invention. As discussed above, Huber relates to a ***compressed tablet***, which is ***free of water***. This tablet is a relatively dense structure which is formulated specifically for oral administration and digestion within the stomach and gastrointestinal tract. Morella et al. also relates to an oral tablet for sustained release via stomach digestion. Morella's tablet contains an ***inner core and an outer coating***; the coating is formulated specifically for fast dissolution, but nowhere does it indicate that the outer coating should be utilized for fast release of drug. Furthermore, the process of making the Morella et al. product are specifically dried [col. 13, l. 1-3], which precludes its being subject to freeze-drying and lyophilization.

As posited in applicants' paper dated December 10, 2001, Morella et al. appears to have been cited solely for the proposition that metronidazole can be used in a pharmaceutical composition in substitution for nitrofurantoin as described by Huber.

However, even in combination with Huber, one of ordinary skill in the art would not have reached the compositions of applicants' invention based upon Morella et al. because neither describes a product that is suitable for freeze-drying nor does either suggest such a product.

Nor would the Conte et al. nor the Saslawski et al. references have compensated for the deficiencies of the Huber and Morella et al. patents in motivating one of ordinary skill in the art to arrive at the compositions of applicants' invention. Conte et al. also relates to ***tablets*** which may effervesce at varying rates to provide a rapid release and a slower, sustained release. Such tablets are, again, ***dry*** and would not have been able to be freeze-dried and lyophilized.

The Saslawski et al. reference relates to ***a bilayer tablet*** "comprising at least two superposed layers, characterized in that: a first outer layer is composed of a mixture of excipients and of a first active substance...the second layer, arranged in contact with the said first layer, consists of a nonbiodegradable, inert porous polymeric matrix in which a second active substance is dispersed." [Saslawski, p. 1, Abstract]. Thus, the Saslawski tablet contains an outer layer and an inner layer which are compressed [Saslawski, p. 21, l. 19-35]. As with the other compressed tablet structures, that of Saslawski would not have been subject to freeze-drying as it has no water present in the structure. Neither reference suggests or describes a freeze-dried composition nor a combination of any freeze-dried layer with another layer to attain a dual-rate release composition. Thus, the Conte et al. and Saslawski et al. references, even in combination with Huber and Morella et al., would not have driven one of ordinary skill in the art toward the freeze-dried controlled release compositions of applicants' invention.

Nor does Gole et al. compensate for the insufficiencies of the combination of Huber, Morella et al., Conte and Saslawski et al. in directing one of ordinary skill in the art toward the compositions of applicants' invention. Gole et al. relates to a solid freeze-dried dosage form which dissolves quickly [col. 2, l. 39-45 and 54-55] and a method for making such a dosage form. Gole et al. describes homogeneous dosage forms and nowhere suggests or describes the use of such quickly dissolving compositions in combination with another, sustained release layer. Nor does Gole et al. motivate one of ordinary skill in the art to combine its teachings with Huber or Morella et al. in order to reach the compositions of applicants' invention.

First, the Huber, Morella et al., Conte and Saslawski et al. references describe either only compressed solid tablets or other tablets that are free of water and would not motivate one of ordinary skill in the art to combine these compositions with lyophilized compositions. Second, the problems inherent in freeze-drying would discourage even one of ordinary skill in the art familiar with lyophilization to attempt to construct a multi-layer composition and be able to attain a usable dosage form. Freeze-drying often results in cracking due to stresses during ice crystallization or meltback, even when a homogeneous type of substrate is used. Thus, one would not expect a composition containing two or more distinct types of compositions in one multilayered unit to achieve a cohesive product. Such a structure would have been expected to crack due to the stresses resulting from different reactions to the lyophilization process. Further, the disparate ingredients might have been expected to have different melting and freezing properties.

Nor would one expect, in light of Gole et al., that a composition containing two freeze-dried layers would result in a dual-rate release composition. Thus, there is no motivation to combine Huber, Morella et al. and Gole et al. in order to produce a composition according to applicants' invention.

Applicants therefore request reconsideration of the rejection of the claims under 35 U.S.C. 103(a) over Huber in view of Morella et al., Conte et al., Saslawski et al. and Gole et al.

In view of the foregoing discussion, applicants respectfully request reconsideration of the rejections set forth in the Final Rejection of February 4, 2002. Entry of this Amendment and an early allowance is earnestly solicited.

Respectfully submitted,

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APPENDIX: MARKED-UP CLAIMS

1. (Thrice Amended) A freeze-dried composition comprising:

(a) a sustained release layer comprising:

(i) a water-soluble polymer; and

(ii) a first pharmaceutically active agent; and

(b) a fast release layer comprising:

(i) a matrix forming agent; and

(ii) a second pharmaceutically active agent;

[(iii)]

said composition being made by the process comprising:

(a) adding said water-soluble polymer and said first pharmaceutically active agent to water to form a first aqueous solution;

(b) adding said matrix forming agent and said second pharmaceutically active agent to water to form a second aqueous solution;

(c) combining said first and said second aqueous solutions in a container to form a combined solution;

(d) rapidly freeze-drying said combined solution; and

(e) lyophilizing said combined solution.

7. (Amended) A composition as defined in claim 1, wherein the sustained release layer further comprises [(iii)] a fatty acid.

8. (Amended) A composition as defined in claim [1] 7, wherein the fatty acid is a hydrogenated vegetable oil.

56. (Amended) A freeze-dried pharmaceutical composition comprising;

(a) a sustained release layer comprising:

(i) a water-soluble polymer; and

(ii) a first pharmaceutically active agent; and

(b) a fast release layer comprising:

(iii) a matrix forming agent; and

(iv) a second pharmaceutically active agent

said composition being made by the process comprising:

(a) adding said water-soluble polymer and said first pharmaceutically active agent to water to form a first aqueous solution;

(b) adding said matrix forming agent and said second pharmaceutically active agent to water to form a second aqueous solution;

(c) combining said first and said second aqueous solutions in a container to form a combined solution;

(d) rapidly freeze-drying said combined solution; and

(e) lyophilizing said combined solution.

65. (Amended) A freeze-dried pharmaceutical composition comprising:

(a) a sustained release layer comprising:

(i) a water-soluble polymer selected from the group consisting of celluloses, cellulose ethers, polycarboxylated vinyl polymers, polyurethanes, gelatins, polysaccharide gums, seed gums, crosslinked [laginate] alginate gum gels and any combination of the foregoing; and

(ii) a first pharmaceutically active agent selected from the group consisting of metronidazole, miconazole nitrate, terconazole, chlorpheniramine maleate, pseudophedrine, dextromethorphan, meclizine [dihydroxhloride] dihydrochloride, haloperidol, albuterol sulfate, dimenhydrinate, benzodiazepines, and any combination of any of the foregoing; and

(b) a fast release layer, comprising:

(i) a matrix forming agent selected from the group consisting of animal and vegetable protein derivatives, gums, polysaccharides, alginates, carboxymethylcelluloses, carrageenans, dextrans, pectins, polyvinylpyrrolidone, polyacrylic acid, polypeptide/protein [compexes] complexes, sugars, inorganic salts, amino acids having from about 2 to about 12 carbon atoms, and any combinations of any of the foregoing; and

(ii) a second pharmaceutically active agent, selected from the group consisting of [metrondazole] metronidazole, terconazole, miconazole nitrate, chlorpheniramine maleate, pseudophedrine, dextromethorphan, meclizine [dihydroxhloride] dihydrochloride, haloperidol, albuterol sulfate, dimenhydrinhate, benzodiazepines, and any combination of any of the foregoing;

said composition being made by the process comprising:

(a) adding said water-soluble polymer and said first pharmaceutically active agent to water to form a first aqueous solution;

(b) adding said matrix forming agent and said second pharmaceutically active agent to water to form a second aqueous solution;

(c) combining said first and said second aqueous solutions in a container to form a combined solution;

(d) rapidly freeze-drying said combined solution; and

(e) lyophilizing said combined solution.

66. (Amended) A freeze-dried pharmaceutical vaginal suppository composition comprising:

(a) a sustained release layer, comprising:

(i) from about 5 to about 70% by weight of a water-soluble polymer;

(ii) from about 15 to about 95% by weight of a first pharmaceutically active agent; and

(b) a fast release layer, comprising:

(i) from about 0.5 to about 15% by weight of a matrix forming agent; and

(ii) from about 85 to about 99.5% by weight of a second pharmaceutically active agent;

said composition being made by the process comprising:

(a) adding said water-soluble polymer and said first pharmaceutically active agent to water to form a first aqueous solution;

(b) adding said matrix forming agent and said second pharmaceutically active agent to water to form a second aqueous solution;

(c) combining said first and said second aqueous solutions in a container to form a combined solution;

(d) rapidly freeze-drying said combined solution; and

(e) lyophilizing said combined solution.